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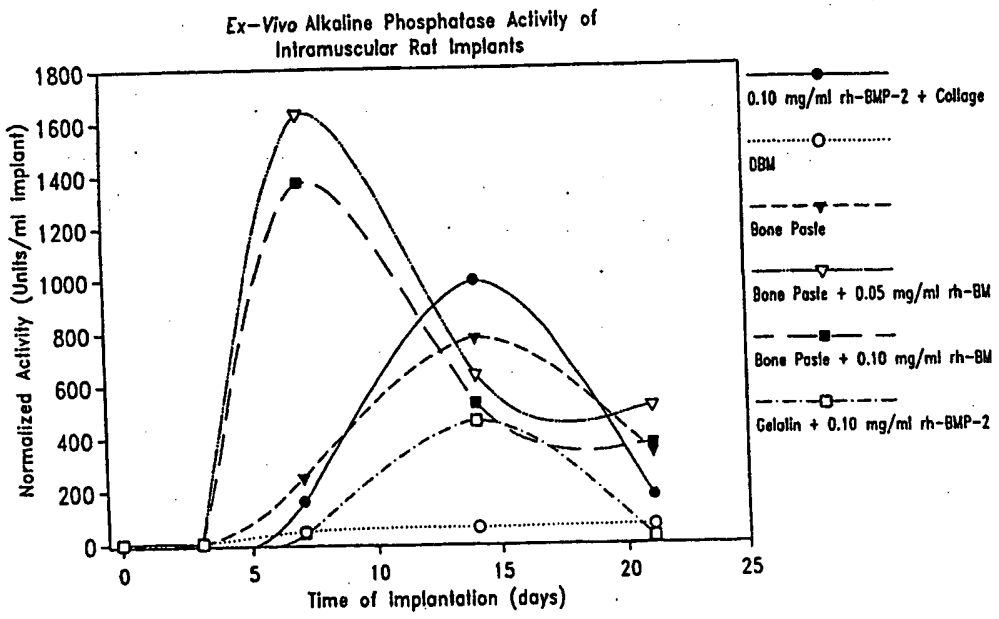

(57) Abstract

Described are osteogenic paste compositions with enhanced osteoinductive properties for use in bone repair. Compositions comprising a quickly resorbable paste carrier, a more slowly resorbed mineral matrix, and Bone Morphogenetic Protein (BMP) or other osteogenic factor are described which enable increased osteoinductive activity while retaining a reliable scaffold for the formation of new bone at the implant site. Methods for making and methods for therapeutic use of the compositions are also disclosed.

OSTEOGENIC PASTE COMPOSITIONS AND USES THEREOF

REFERENCE TO RELATED APPLICATION

This application claims the benefit of U.S. Patent Application Serial No. 60/118,614 filed February 4, 1999, which is hereby incorporated by reference in its entirety.

FIELD OF INVENTION

The present invention relates generally to osteogenic paste compositions containing a paste-form carrier and an osteogenic factor. In one specific aspect, this invention relates to osteogenic paste compositions containing a paste-form carrier, an osteogenic factor, and a substantial mineral component to provide a lasting scaffold for bone growth. This invention also relates to methods of making and using the osteogenic paste compositions.

BACKGROUND

As further background, bone grafting is commonly used to augment healing in the treatment of a broad range of musculoskeletal disorders. Grafting has been effective in reconstruction or replacement of bone defects, to augment fracture repair, to strengthen arthrodeses and to fill defects after treatment of tumors. Autograft techniques have been known for over 100 years and include the use of cortical and cancellous bone as grafting material. The use of autografts presents several serious drawbacks including the limited amount of potential donor material available, the requirement for two surgical intrusion sites on the patient, a high incidence of donor site morbidity, the tedious and complex nature of the techniques, particularly when vascularized grafts are involved, and the fact that donated bone can rarely be precisely sized or shaped to fit the needs of the implant site. Allografts can also be used in analogous procedures. Allografts have the benefits of avoiding

porosity. TCP is degraded 10-20 times faster than hydroxyapatite. Also partly as a result, if new bone development is established with a TCP implant, the TCP is generally remodeled better than hydroxyapatite in the final stage of bone formation. It is noteworthy that TCP is resorbed by osteoclast cells, whereas, the much slower resorption of hydroxyapatite is effected mainly by foreign-body giant cells. The giant cells have a limit as to the amount of hydroxyapatite they will resorb.

Pure ceramics do not offer optimum handling characteristics during implantation, but do offer excellent biocompatibility properties and tend to bond well to the existing bone. Ohgushi, et al. teaches the use of marrow infiltration of ceramics, while others have used various binders with granulated ceramics to formulate workable pastes that solidify to provide stable implants of desired shape and size. C.P. Desilets, L.J. Marden, A.L. Patterson and J.O. Hollinger, *Development of synthetic bone-repair materials for craniofacial reconstruction*, J. Craniofacial Surgery, Vol. 1(3), 1990, pg. 150-153.

Demineralized bone matrix (DBM) preparations have been researched extensively for use as bone implant material. DBM is prepared through the acid extraction of minerals from bone. It includes the collagen matrix of the bone together with acid insoluble proteins including bone morphogenic proteins (BMPs) and other growth factors. DBM can be processed as crushed granules, powder or chips. It can be formulated for use as granules, gels, sponge material or putty and can be freeze-dried for storage. Sterilization procedures required to protect from disease transmission may reduce the activity of beneficial growth factors in the DBM. DBM provides an initial osteoconductive matrix and exhibits a degree of osteoinductive potential, inducing the infiltration and differentiation of osteoprogenitor cells from the surrounding tissues. DBM lacks structural strength and is therefore only useful to fill well

implant must therefore be carefully retained in place until the composite and any surrounding bleeding has fully clotted.

Compositions of bone gel known as GRAFTON® (see U.S. Patent No. 5,481,601) comprising glycerol and DBM have been used singly and mixed with sand-like powder. Such compositions have been used to fill bone voids, cracks and cavities. GRAFTON® is available in flexible sheets or as a putty, thus making the composition more easily workable during implantation. Again, such compositions tend to flow away from the implant site.

Jefferies, in U.S. Patent 4,394,370 and 4,472,840, teach a bone implant material composition of collagen and DBM or solubilized BMP that is optionally crosslinked with glutaraldehyde.

Caplan et al., in U.S. Patent 4,620,327, describe the combination and partial immobilization by chemical cross-linking of soluble bone proteins with a number of solids to be implanted for bone repair/incorporation, including xenogenic bony implants, allografts, biodegradable masses and prosthetic devices to enhance new bone or cartilage formation. Ries et al., in U.S. Patent 4,623,553, describe the glutaraldehyde or formaldehyde cross-linking of collagen and hydroxyapatite or TCP. Ries does not include any osteoinductive elements and is deemed only osteoconductive.

Some researchers have suggested the use of composites of TCP and/or biopolymers like polylactide, polyglycolide or their copolymers and particulate bone derivatives or BMP for craniofacial reconstruction. The TCP and biopolymers would provide a scaffold for new bone formation. The bone derivatives and BMP would induce osteogenesis

SUMMARY OF THE INVENTION

The present invention generally provides osteogenic paste compositions including a paste-form carrier such as a gelatin paste and at least one osteogenic factor such as BMP-2 or another similar bone morphogenetic protein. A particular feature of the present invention relates to the discovery that the inclusion of an osteoblast- and osteoclast-stimulating osteogenic factor in a paste-form composition including a resorbable paste carrier causes a rapid and premature resorption of the carrier. This rapid resorption of the carrier can diminish or eliminate the capacity of the paste-form composition to effectively stimulate and support new bone formation in a void filled with the composition. This is particularly the case in primates, including humans, in which the rate of new bone formation is relatively slow.

Accordingly, one preferred embodiment of the present invention provides an osteogenic paste composition effective for the induction and support of new bone growth in a primate. The implant composition comprises a resorbable paste-form carrier, including for instance a paste made with a substance such as gelatin, hyaluronic acid, and/or carboxymethyl cellulose. The composition also includes an effective amount of an osteogenic factor, such as a bone morphogenetic protein, that stimulates both osteoblast cells and osteoclast cells. In addition, composition includes a substantial proportion of a particulate mineral that is effective to provide a scaffold for bone ingrowth when the resorbable paste carrier is resorbed at an increased rate due to the stimulation of osteoclast cell activity. Preferred such compositions of the invention are provided wherein the resorbable paste carrier includes gelatin, and/or wherein the resorbable paste carrier is flowable at temperatures above the body temperature of the mammal in which it is

In one particularly preferred form of the present invention, an osteogenic paste composition for the induction of new bone growth in a primate is provided, comprising:

(a) a resorbable paste carrier comprising gelatin, the resorbable paste carrier formulated to be flowable at temperatures above the body temperature of the primate, and to transitions to a non-flowable mass at such body temperature;

(b) demineralized bone matrix;

(c) a bone morphogenic protein that stimulates osteoblasts and osteoclasts, more preferably BMP-2 or BMP-7; and

(d) cortical or cancellous bone particles, having an average particle size of between about 0.050 and about 5.0 mm, and constituting about 20% to about 80% by volume of the overall implant composition.

Still other preferred embodiments of the present invention provide methods for treating bone trauma, defect or disease, or for effecting artificial arthrodeses in a mammal, comprising the step of implanting an osteogenic paste composition of the invention in a primate at a site of desired new bone formation.

The present invention provides an improved osteogenic implant material that is strongly osteoinductive and that can be formed into precise shapes either prior to implant or during the surgical procedure itself. The present invention also provides implant materials that retain stable shapes at the implant site and do not deform, migrate, or flow away from the implant site before ossification is established. Significantly, the present invention also provides advantageous implant materials that have enhanced osteoinductive potential and provide a matrix that is workable during implantation, but not resorbed prior to the establishment of bone within the void to be filled. Such preferred compositions provide a mineral scaffold for the generation of new bone

BRIEF DESCRIPTION OF FIGURES

Figure 1 shows *ex vivo* alkaline phosphatase activity as a function of time for intramuscular rat implants of demineralized bone matrix, a paste of gelatin and demineralized bone matrix, and of rhBMP-2 in each of a collagen sponge, a paste of gelatin and demineralized bone matrix, and in a paste of gelatin alone.

Figure 2 shows calcium content of explanted ossicles as a function of time for intramuscular rat implants of demineralized bone matrix, a paste of gelatin and demineralized bone matrix, and of rhBMP-2 in each of a collagen sponge, a paste of gelatin and demineralized bone matrix, and in a paste of gelatin alone.

paste-form osteogenic composition that includes a substantial amount of a relatively slowly-resorbed mineral component that remains at the implant site after the carrier has been rapidly resorbed, in order to provide a scaffold for new bone formation that is not prematurely resorbed due to the osteoclastic potentiation by the bone morphogenic protein in the composition. The present invention also provides methods for using such osteogenic compositions in treatment of bone trauma, disease and defects, for artificial arthrodeses and for other treatment where new bone formation is desired, especially in primates, including humans.

Generally speaking, compositions in accordance with the present invention are in paste form and comprise a resorbable carrier, especially a gelatin paste, and an osteogenic factor such as a BMP that stimulates osteoblasts and osteoclasts, e.g. BMP-2 or BMP-7, especially BMP-2. The preferred compositions of the invention also include a substantial proportion (i.e. at least about 20% by volume) of a particulate, porous mineral matrix dispersed within the carrier. Such compositions can also include other resorbable components, for example demineralized bone matrix.

As to the carrier, in accordance with the present invention, it will be biologically resorbable and will contribute to providing a paste form to the composition allowing its implantation and retention at the candidate site for bone ingrowth. Preferred carriers will include resorbable macromolecules from biological or synthetic sources, for example gelatin, hyaluronic acid carboxymethyl cellulose, collagen, peptides, and the like. In more preferred inventive forms, the resorbable carrier, especially gelatin, is formulated into the composition such that the composition is flowable at temperatures above the body temperature of the mammal into which the material is to be implanted, but

Paste compositions of the invention may also include other potentially osteoinductive substances, including for example demineralized bone matrix (DBM). As is known in the field, DBM can be prepared by acid demineralization of bone and when so prepared contains, among other constituents, the collagen matrix of the bone and acid insoluble proteins. DBM has been shown previously to be mildly osteoinductive by itself and has a favorable porous matrix for the ingrowth of bone. Methods of producing DBM are known in the art and are, therefore not elaborated upon here (see for example U.S. Patent 5,405,390, herein incorporated by reference for this purpose). In a preferred form, DBM having a particle size of between about 0.10 and about 1.00 mm will be incorporated within compositions of the present invention. The DBM can be derived from the same or a different mammalian species as that in which the implant material is to be used. When used, the DBM is preferably blended with the resorbable carrier in a weight ratio between about 1:4 and about 3:2 DBM to resorbable carrier. Commercially available preparations of DBM are suitable for use in the present invention provided they may be uniformly blended with the other elements of the composition.

As indicated above, preferred paste compositions of the invention also include an osteoinductive factor, such as an osteoinductive protein or a nucleotide sequence encoding an osteoinductive protein operably associated with a promoter (e.g. provided in a vector such as a viral vector), for example a bone morphogenetic protein or a gene encoding the same operationally associated with a promoter which drives expression of the gene in the animal recipient to produce an effective amount of the protein. The bone morphogenic protein (BMP) in accordance with this invention is any BMP able to stimulate differentiation and function of osteoblasts and osteoclasts. Examples of such BMPs are BMP-2, BMP-4, and BMP-7, more preferably rhBMP-2 or

suitable manner, for example by pre-impregnating the mineral particles with the osteogenic factor prior to blending with the paste carrier, by blending the factor with the carrier, or both. Alternatively or in addition, amounts of the osteogenic factor can be blended with the carrier/mineral mixture immediately prior to implantation.

The porous mineral used in accordance with the preferred embodiments of the present invention includes a natural or synthetic mineral that is effective to provide a scaffold for bone ingrowth as the resorbable carrier and other more rapidly resorbed elements of the implant composition are resorbed. Illustratively, the mineral matrix may be selected from one or more materials from the group consisting of bone particles, Bioglass®, tricalcium phosphate, biphasic calcium phosphate, hydroxyapatite, corraline hydroxyapatite, and biocompatible ceramics. Biphasic calcium phosphate is a particularly preferred synthetic ceramic for use in the invention. Desirably, such biphasic calcium phosphate with have a tricalcium phosphate:hydroxyapatite weight ratio of about 50:50 to about 95:5, more preferably about 70:30 to about 95:5, even more preferably about 80:20 to about 90:10, and most preferably about 85:15.

In another preferred aspect of the invention, the mineral matrix includes bone particles, possibly cancellous but preferably cortical, ground to provide an average particle diameter between about 0.050 and 5.0 mm. Both human and non-human sources of bone are suitable for use in the instant invention, and the bone may be autographic, allographic or xenographic in nature relative to the mammal to receive the implant. Appropriate pre-treatments known in the art may be used to minimize the risks of disease transmission and/or immunogenic reaction when using bone particles in the mineral matrix.

osteogenic enhancing factors may be incorporated into the composition. Such additional factors include, but are not limited to host compatible osteogenic progenitor cells, autographic bone marrow, allographic bone marrow, transforming growth factor-beta, fibroblast growth factor, platlet derived growth factor, insulin-like growth factor, microglobulin-beta, antibiotics, antifungal agents, wetting agents, glycerol, steroids and non-steroidal anti-inflammatory compounds.

In use, the paste-form implant compositions of the invention are implanted at a site at which bone growth is desired, e.g. to treat a disease, defect or location of trauma, and/or to promote artificial arthrodesis. The paste form of the compositions enables their positioning, shaping and/or molding within voids, defects or other areas in which new bone growth is desired. In the case of implant compositions which are flowable at temperatures higher than the body temperature of the mammal in which they are to be implanted, yet which transition to a non-flowable mass at or near such body temperature, the composition is heated to a temperature at which it is flowable, but which will not denature any osteogenic factor present; molded or otherwise shaped to the shape of the desired new bone; cooled to a temperature sufficient to transition the osteogenic implant material into a non-flowable mass either in situ or implanted at the site of desired new bone formation after setting up. In other preferred situations, the paste composition does not require heating to above body temperature (about 37°C) for flowability, for example wherein the paste composition is flowable at temperatures below 37°C and cures or solidifies into a non-flowable mass upon heating or upon contact with a separate curing agent. Such cases are particularly advantageous in that heat-induced denaturation of the osteogenic factor is less of a concern.

levels of vascularization and thus fusions of these elements are expected to benefit markedly from the invention. In addition, in accordance with other aspects of the invention, the osteogenic paste compositions of the invention can be incorporated in, on or around a load-bearing (e.g. having a compressive strength of at least about 10000 N) implant device such as a fusion cage, dowel, or other device having a pocket, chamber or other cavity for containing an osteogenic composition, and used in a spinal fusion such as an interbody fusion.

The invention will now be more particularly described with reference to the following specific Examples. It will be understood that these Examples are illustrative and not limiting of the invention.

EXAMPLE 1

Rat Study Comparing the Effect of rhBMP-2 on Osteogenic Capacity of a Matrix Consisting of Collagen Derived Gelatin and Demineralized Bone Matrix (DBM).

Thirty young adult male Sprague-Dawley rats weighing between 200-220 g, were randomly assigned to two groups. Each animal was surgically implanted with six 0.050 mL samples. The samples were inserted in pockets incised into the rectus abdominus muscles on either side of the midline. Samples were placed three to a side, evenly spaced in lines extending from below the sternum to above the mid-groin.

Two of the six samples for each animal were positive controls, one being DBM alone, the second being Helistat® Absorbable Collagen Sponge (ACS) onto which 0.004 mg rhBMP-2 had been adsorbed. Group I animals were also given duplicate samples of a gelatin/DBM injectable matrix (Gelatin Bone Paste) and duplicate samples of the

do not incorporate mineral matrix elements to provide prolonged scaffolding for the bone formation process. It should be noted that the ACS controls containing 0.004 mg rhBMP-2 and the gelatin samples containing 0.002 mg rhBMP-2 had the most readily resorbable matrices and gave the poorest calcification performances for samples containing rhBMP-2. See figure 2.

EXAMPLE 2

Monkey Study Comparing Osteogenicity of rhBMP-2 Containing Implant Matrices.

Studies in a monkey spinal fusion model were conducted to determine the effectiveness of three paste compositions. The compositions were the gelatin bone paste of Example 1, that paste containing autograft bone chips, and that paste containing rhBMP-2 at a single level of the spine. Each composition was used in bilateral fusion of vertebra in rhesus monkeys and analyzed for its ability to induce new bone formation. In doing so, CT scans were taken every two months over a six-month period. The results demonstrated variable bone growth in monkeys receiving the paste of Example 1 alone and in the paste containing autograft bone chips, but no growth in monkeys receiving the paste and rhBMP-2. This observation is expected to be due to the premature resorption of the carrier in the rhBMP-2-containing paste, leaving no matrix for bone ingrowth. Accordingly, incorporation of a substantial mineral component in a BMP-containing paste in accordance with the present invention will provide a lasting matrix and scaffold for bone ingrowth, thus improving performance.

WHAT IS CLAIMED IS:

1. An osteogenic paste composition effective for the induction of new bone growth in a primate, comprising:

a resorbable paste carrier;

an osteogenic factor; and

a porous particulate mineral in an amount of at least 20% by volume of the composition, said amount being effective to provide a scaffold for bone ingrowth as the resorbable paste carrier is resorbed.

2. The composition of claim 1 which further comprises demineralized bone matrix.

3. The composition of claim 2 wherein the ratio of demineralized bone matrix to resorbable carrier is between about 1:4 and about 3:2 by weight.

4. The composition of claim 2 wherein the composition comprises 5-45% by weight resorbable carrier.

5. The composition of claim 1 wherein the resorbable carrier is flowable at temperatures above the body temperature of the mammal, but transitions to a non-flowable mass at or slightly above said body temperature.

6. The composition of claim 1 wherein the mineral is selected from the group consisting of bone particles, bioglass, tricalcium phosphate, hydroxyapitite, corraline hydroxyapitite, biocompatible ceramic and non-resorbable biocompatible organic polymer.

13. An osteogenic implant material effective for the induction of new bone growth in a mammal, comprising:

a resorbable paste carrier comprising gelatin, the resorbable carrier formulated to be flowable at temperatures above the body temperature of the mammal, and to transition to a non-flowable mass at said body temperature;

demineralized bone matrix;

an osteogenic factor; and

a particulate mineral having an average particle size of about 0.050 to about 5.0 mm, said mineral constituting at least 20% by volume of said composition.

14. The composition of claim 13 wherein the mineral constitutes about 20% to about 80% by volume of the composition.

15. The composition of claim 13 wherein the mineral comprises human bone particles.

16. The composition of claim 13 wherein the mineral comprises non-human bone particles, said particles having been treated to reduce their immunogenicity in humans.

17. The composition of claim 13 wherein the osteogenic factor is a bone morphogenic protein selected from BMP-2, BMP-4, BMP-6 and BMP-7, a LIM mineralization protein, or a nucleotide sequence encoding said bone morphogenic protein or LIM mineralization protein.

18. A method for inducing bone growth in a primate, comprising implanting in the primate a composition according to claim 1, at a site at which bone growth is desired.

particulate mineral effective to provide a scaffold for bone ingrowth as the resorbable carrier is resorbed, said mineral constituting at least 20% by volume of the paste composition;

implanting said osteogenic paste composition at a site of desired new bone formation; and

cooling the osteogenic paste composition to a temperature sufficient to transition the osteogenic paste composition to a non-flowable mass.

28. The method of claim 27 wherein the implant material further comprises demineralized bone matrix.

29. The method of claim 27 wherein the primate is a human.

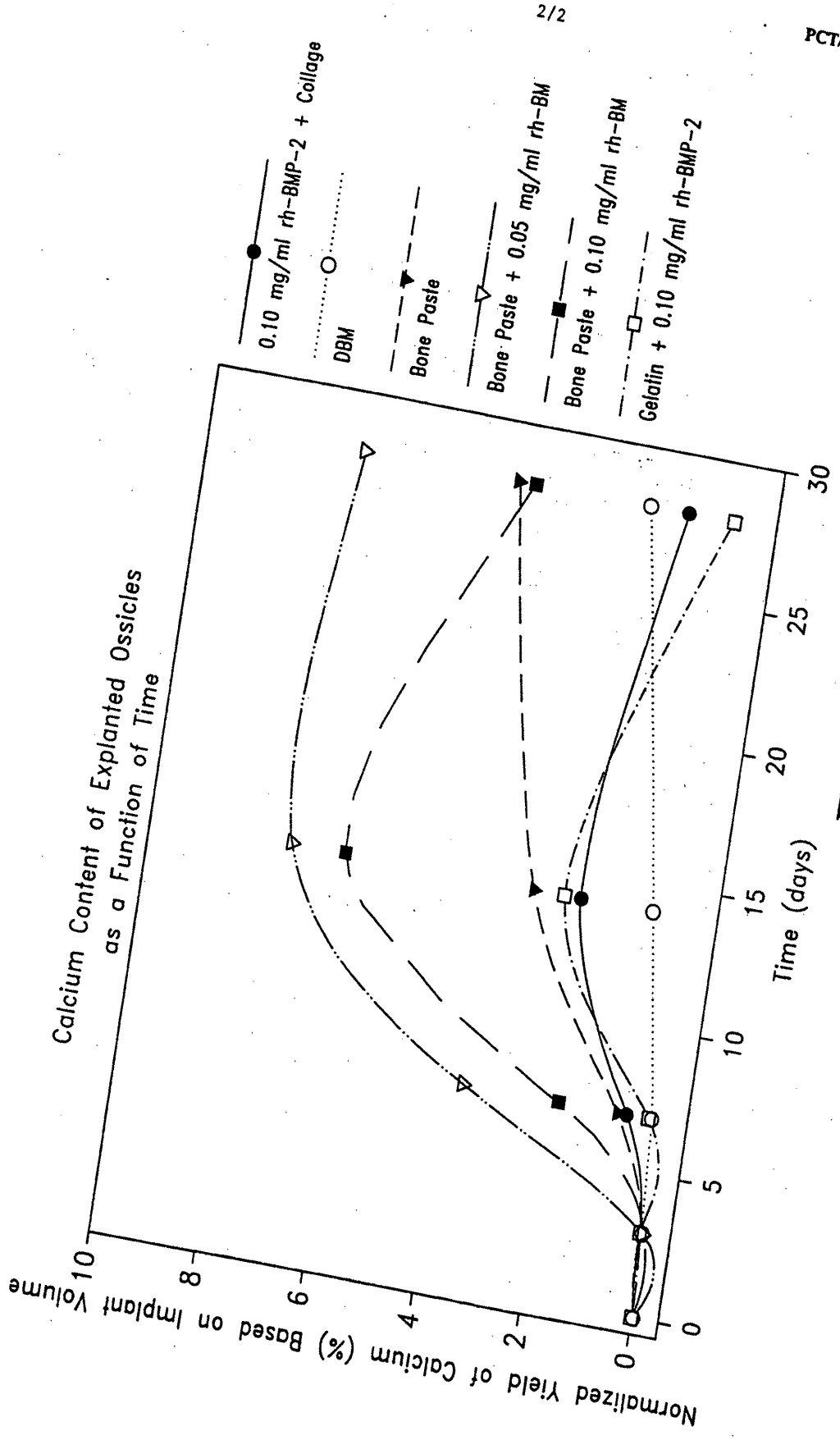
Calcium Content of Explanted Ossicles
as a Function of Time
Normalized Yield of Calcium (%) Based on Implant Volume
Time (days)
0
2
4
6
8
10
0
5
10
15
20
25
30
0.10 mg/ml rh-BMP-2 + Collage
DBM
Bone Paste
Bone Paste + 0.05 mg/ml rh-BM
Bone Paste + 0.10 mg/ml rh-BM
Gelatin + 0.10 mg/ml rh-BMP-2

Fig. 2

INTERNATIONAL SEARCH REPORT

International Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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